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| EXAMINER | |
|---|---|
| ISSAC, ROY P | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/767,019 | WRIGHT, GEORGE E. | |
| | Examiner | Art Unit | |
| | Roy P. Issac | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19 and 32-42* is/are pending in the application.

4a) Of the above claim(s) *41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 & 32-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/03/2004 & 8/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This application claims priority under 35 U.S.C § 119(e) from the provisional application 60/443,519 filed 01/29/2003.

### *Election/Restrictions*

Applicant's election without traverse of invention of Group I, claims 1-19 and 32-36, and the addition of new claims 37-42, and the cancellation of claims 20-31, in the reply filed on 03/15/2007 is acknowledged.

Newly submitted claims 41-42 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Newly submitted claims 41-42 directed to a method of treating Herpes simplex virus. The newly submitted claims 41-42 are related to the elected invention I, claims 1-19 and 32-36 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the process of using the product as claimed can be practiced with a materially different product. There are several ways to treat herpes infection. For example, antiviral creams such as iodoxuridine and triflurindine can be used to treat herpes simplex infection. The antiviral agent, acyclovir itself can also be used to treat herpes simplex infection.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 41-42 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Of the newly added claims, claims 37-40 directed to kits comprising antiherpes substances are grouped with the elected group I and are examined on the merits herein.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement between inventions of Groups I and II, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria

for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The restriction requirement between Inventions I and II was deemed proper and is therefore made FINAL.

Claims 41-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-19 and 32-40 will be examined on the merits herein.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 and 32-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation, "analog" in these claims render claims herein indefinite. The recitations, "analog" of the compounds are not clearly defined in the specification. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "analog" of compounds herein. One of ordinary skill in the art would clearly recognize that analog of a nucleoside or a pyrophosphate or phosphonate nucleoside analog would read on any those compounds having any widely varying groups that possibly substitute the compounds.

Any significant structural variation to a compound would be reasonably expected to alter its properties; e.g., physical, chemical, physiological effects and functions. Thus, it is unclear and indefinite as to the "analog" of compounds herein encompassed thereby.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 and 32-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for one of a composition comprising 2-phenylamino-6-oxo-9-(4-hydroxybutyl)purine, (HBPG) and foscarnet or acyclovir or cidoforvir, does not reasonably provide enablement for the use of a combination of any inhibitor of Herpes simplex virus thymidine kinase with **any** antiherpes substance comprising one or more of a (1) a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog and a nucleoside analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to the method for the treatment of disorders associated with calcium homeostasis. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The claimed invention is a therapeutic method for preventing or treating a herpes simplex viral infection using combination therapy.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The breadth of the claims:

The current claims are deemed very broad since they include the combination of any that is an inhibitor of Herpes simplex virus thymidine kinase and any one of the large classes of compounds selected from one of the large classes of drugs encompassed by the descriptions pro-phosphorylated or phosphonate nucleoside analog, or pyrophosphoate analog or nucleoside analog or any combination thereof or an ester salt or solvate thereof. The compound to be combined includes all known drugs used for the treatment of said diseases as well as the ones to be developed in the future.

The amount of direction or guidance presented and the presence or absence of working examples:

There are only three working examples of combination therapy provided. Table 2 (Page 13, line 35 to page 14, line 8) describes the efficacy of a combination of HBPG with foscarnet. Each of the examples discloses a

combination of HBPG with one of the three well known antiherpes agents. The broad claims herein are directed to a combination of a broad class of compounds with any one or more of the compounds selected from another three broad classes of compounds. As such, the disclosure of the working examples is not commensurate with the claims herein. For example, no representative from the class of pyrophosphate analog is shown as a working example in combination with an inhibitor of Herpes simplex virus thymidine kinase.

The predictability or lack thereof in the art and the quantity of experimentation necessary:

Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects, which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions

between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10$^{th}$ Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56. (PTO-892) Thus, the teachings of the book clearly support that the instant claimed invention, administering a combination of an inhibitor of Herpes Simplex virus thymidine kinase and an antiherpes substance comprising one or more of a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog and a nucleoside analog.

The usefulness of HBPG with one of the three compounds does not mean that any compound with activity as inhibitor of Herpes simplex virus thymidine kinase will be useful for combination therapy with one or more of a compound selected from the classes of compounds considered as a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog and a nucleoside analog.

In particular, one skilled in the art would need to know whether the regular administration of the combination in the claimed form over the long term would adversely affect the health of the subject.

In order to answer these questions, in the absence of any existing data, one skilled in the art, will have to undertake laboratory and clinical studies involving different combinations of one of the broad class of compounds with activity against Herpes simplex virus thymidine kinase and one of any of a large series of compounds selected from pre-phosphorylated or phosphonate nucleoside analogs, a pyrophosphate analogs and nucleoside analogs. Accomplishing such a task for the treatment of herpes infection will require an undue amount of experimentation for the practice of full range of the claimed invention.

*Genetech*, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the combination therapy claimed herein absent undue experimentation.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 and 32-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et. al. (U.S. Patent No. 5,646,155; PTO-1449 dated 5/3/2004) in view of Naesens et. al. (Herpes, 8(1), 2001; PTO-892).

Wright discloses a pharmaceutical composition for the treatment of herpes virus infection comprising an inhibitor of Herpes simplex virus thymidine kinase wherein one of the compounds may be a 6-oxo (guanine) compound (col. 7, line 66 - col. 8, line 5). Wright also teaches that the compound(s) may be combined with other direct antiviral drugs (col. 9, lines 59-62) and may be administered in a variety of formulations (col. 9, lines 16-57).

Wright does not expressly disclose any particular combination of an inhibitior of Herpes simplex virus thymidine kinase and another antiherpes substance or a kit comprising said combination.

Naesens discloses a series of antiherpes substances including acyclovir, ganciclovir, cidofavir, foscarnet and brividin. (Abstract; Pages 13-15). Naesens discloses Foscarnet and cidofovir as antiherpes agents independent of thymidine kinase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising a combination of an inhibitor of Herpes Simplex virus thymidine kinase and an antiherpes substance comprising one or more of a (1) a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog and a nucleoside analog since Wright et. al. discloses pharmaceutical compositions comprising a herpes simplex virus thymidine kinase inhibitor and suggests the combination with other direct antiviral drugs.

One of ordinary skill in the art would have been motivated to make a combination of an inhibitor of herpes simplex thymidine kinase and another antiherpes agent since Wright suggests combination of a oxo-guanine thymine kinase inhibitor with other antiherpes agents.

Therefore, one of ordinary skill in the art would have reasonably expected that the combination of an inhibitor of herpes simplex thymidine kinase and another antiherpes agent would have resulted in substantially similar or beneficial effects in the treatment of herpes infection.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. Furthermore, one of ordinary skill in the art would have been motivated to prepare a kit comprising the same composition because the preparation of a kit comprising a pharmaceutical

composition is considered well in the competence level of an ordinary skilled artisan and well within conventional skills in pharmaceutical science, involving merely routine skill in the art.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

6/7/07

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